Amendments to the Specification

Please replace the paragraph on page 4, starting at line 15, with the following amended paragraph:

In another embodiment, the PGC-1 nucleic acid molecule encodes a dominant negative PGC-1 polypeptide. In one embodiment the dominant negative polypeptide has a mutated LXXLL motif (SEQ ID NO.:3), *e.g.*, wherein at least one of the leucine residues of the LXXLL motif (SEQ ID NO.:3) is substituted with another amino acid residue, for example alanine. In a preferred embodiment, the leucine residue at the fourth position of the LXXLL motif (SEQ ID NO.:3) is substituted with alanine. In another embodiment, the LXXLL motif (SEQ ID NO.:3) is deleted.

Please replace the paragraph on page 4, starting at line 28, with the following amended paragraph:

In another embodiment, the PGC-1 polypeptide is a dominant negative PGC-1 polypeptide. In one embodiment the dominant negative polypeptide has a mutated LXXLL motif (SEQ ID NO.:3), *e.g.*, wherein at least one of the leucine residues of the LXXLL motif (SEQ ID NO.:3) is substituted with another amino acid residue, for example alanine. In a preferred embodiment, the leucine residue at the fourth position of the LXXLL motif (SEQ ID NO.:3) is substituted with alanine. In another embodiment, the LXXLL motif (SEQ ID NO.:3) is deleted.

Please replace the paragraph on page 6, starting at line 22, with the following amended paragraph:

In another embodiment, the PGC-1 nucleic acid molecule encodes a dominant negative PGC-1 polypeptide. In one embodiment the dominant negative polypeptide has a mutated LXXLL motif (SEQ ID NO.:3), *e.g.*, wherein at least one of the leucine residues of the LXXLL motif (SEQ ID NO.:3) is substituted with another amino acid residue, for example alanine. In a preferred embodiment, the leucine residue at the fourth position of the LXXLL motif (SEQ ID NO.:3) is substituted with alanine. In another embodiment, the LXXLL motif (SEQ ID NO.:3) is deleted. In another embodiment, the PGC-1 nucleic acid molecule is an antisense PGC-1 nucleic acid molecule.

Please replace the paragraph on page 11, starting at line 14, with the following amended paragraph:

Alternatively, if it is desirable to treat a disease or disorder characterized by (or associated with) aberrant or abnormal (non-wild-type) PGC-1 nucleic acid expression and/or PGC-1 protein activity by inhibiting PGC-1 protein activity, a PGC-1 modulator can be an anti-PGC-1 antibody or a small molecule or other drug, *e.g.*, a small molecule or drug identified using the screening assays described herein, which inhibits PGC-1 protein activity. In a preferred embodiment, a PGC-1 modulator is a PGC-1 dominant negative, *e.g.*, a PGC-1 polypeptide wherein the LXXLL motif (SEQ ID NO.:3) is deleted or mutated, or a PGC-1 nucleic acid molecule which encodes a PGC-1 polypeptide wherein the LXXLL motif (SEQ ID NO.:3) is deleted or mutated.

Please replace the paragraph beginning on page 23, starting at line 12, and continuing onto page 24, with the following amended paragraph:

In another embodiment, a PGC-1 nucleic acid molecule encodes a PGC-1 protein which is a "dominant negative". As used herein, the "dominant negative" refers to a protein or polypeptide, or the nucleic acid molecule which encodes it, that, when expressed in a cell, inhibits the activity of its wild type homologue (*e.g.*, the endogenous gene or an exogenously supplied wild type homologue). For example, in a preferred embodiment, a dominant negative PGC-1 molecule is one which, when expressed in a cell (*e.g.*, a liver cell), inhibits at least one or more activities (as described herein) of the wild type PGC-1 gene. In a preferred embodiment, a dominant negative PGC-1 molecule downregulates gluconeogenesis, either partially or completely. In another preferred embodiment, a dominant negative PGC-1 molecule is incapable of binding to HNF-4α but is still capable of binding to other transcription factors, *e.g.*, general transcription factors. Such a dominant negative acts via "squelching". As used herein, the term "squelching" refers to a process by which a dominant negative molecule is expressed at a level such that it binds the majority of certain transcription factors in a cell, leaving none available to bind to the wild-type molecule, effectively rendering the wild type molecule inactive. Depending on the degree of downregulation desired, different dominant negative forms of PGC-1 can be produced which inhibit wild type PGC-1 activities at different levels. In a preferred embodiment, a dominant negative PGC-1 polypeptide comprises a sequence of SEQ ID NO:2 or SEQ ID NO:5, wherein the LXXLL motif (SEQ ID NO:3) is mutated. In one embodiment, one

or more of the leucine residues of the LXXLL motif (SEQ ID NO.:3) can be substitute with an alternate amino acid residue (*e.g.*, alanine) such that the mutated LXXLL motif no longer mediates binding to HNF-4α or to nuclear receptors. In a preferred embodiment, the leucine residue at the fourth position of the LXXLL motif (SEQ ID NO.:3) is substituted with alanine. In another embodiment, at least 1, 2, 3, 4, or 5 amino acid residues of the LXXLL motif (SEQ ID NO.:3) are deleted. The mouse LXXLL (SEQ ID NO.:3) can be found at amino acid residues 142-146 of SEQ ID NO:2 (encoded by nucleotides 515-529 of SEQ ID NO:1), while the human LXXLL motif (SEQ ID NO.:3) can be found at amino acid residues 144-148 of SEQ ID NO:5 (encoded by nucleotides 518-532 of SEQ ID NO:4) (SEQ ID NO.:3). Preferably, a PGC-1 polypeptide with a mutated or deleted LXXLL motif (SEQ ID NO.:3) is incapable of binding to HNF-4α (see Example section).

Please replace the paragraph on page 26, starting at line 12, with the following amended paragraph:

In addition to naturally-occurring allelic variants of the PGC-1 sequence that may exist in the population, the skilled artisan will further appreciate that changes can be introduced by mutation into the nucleotide sequence of SEQ ID NO:1 or SEQ ID NO:4, thereby leading to changes in the amino acid sequence of the encoded PGC-1 protein, without altering the functional ability of the PGC-1 protein. For example, nucleotide substitutions leading to amino acid substitutions at "non-essential" amino acid residues can be made in the sequence of SEQ ID NO:1 or SEQ ID NO:4. A "non-essential" amino acid residue is a residue that can be altered from the wild-type sequence of PGC-1 (*e.g.*, the sequence of SEQ ID NO:2 or SEQ ID NO:5) without altering the activity of PGC-1, whereas an "essential" amino acid residue is required for PGC-1 activity. For example, amino acid residues involved in the interaction of PGC-1 to HNF-4α (*e.g.*, those present in an LXXLL motif (SEQ ID NO.:3)) are most likely essential residues of PGC-1. Other amino acid residues, however, (*e.g.*, those that are not conserved or only semi-conserved between mouse and human) may not be essential for activity and thus are likely to be amenable to alteration without altering PGC-1 activity. Furthermore, amino acid residues that are essential for PGC-1 functions related to thermogenesis and/or adipogenesis, but not essential for PGC-1 functions related to gluconeogenesis, are likely to be amenable to alteration.

Please replace the paragraph on page 43, starting at line 16, with the following amended paragraph:

In a preferred embodiment, the PGC-1 polypeptide is a dominant negative, as described herein. In one embodiment, a dominant negative PGC-1 polypeptide comprises an amino acid sequence of SEQ ID NO:2 or SEQ ID NO:5, wherein the LXXLL motif (*e.g.*, amino acid residues 142-146 of SEQ ID NO:2 or amino acid resides 144-148 of SEQ ID NO:5, also set forth as SEQ ID NO:3) is mutated. In one embodiment, one or more of the leucine residues of the LXXLL motif (SEQ ID NO.:3) can be substituted with an alternate amino acid residue (*e.g.*, alanine) such that the mutated LXXLL motif (SEQ ID NO.:3) no longer mediates binding to HNF-4α or to nuclear receptors. In a preferred embodiment, the leucine residue at the fourth position of the LXXLL motif (SEQ ID NO.:3) is substituted with alanine. In another embodiment, at least 1, 2, 3, 4, or 5 amino acid residues of the LXXLL motif (SEQ ID NO.:3) are deleted.

Please replace the title of EXAMPLE 6 on page 83, with the following amended title:

PHYSICAL INTERACTION WITH HNF-4α REQUIRES THE LXXLL MOTIF (SEQ ID NO.:3) IN THE AMINO TERMINUS OF PGC-1

Please replace the paragraph beginning on page 83, starting at line 28, and continuing on page 84, with the following amended paragraph:

Because the LXXLL sequence (SEQ ID NO:3) located at amino acid residues 142-146 of PGC-1 (SEQ ID NO:2) had been found to be required for the binding of PGC-1 to ERα and PPARα, a mutant construct of amino acid residues 1-190 of SEQ ID NO:2, in which the LXXLL (SEQ ID NO:3) sequence was mutated by substituting the leucine residue at the fourth position with alanine, was also tested. Radiolabeled HNF-4α protein was produced by *in vitro* translation with [^{35}S]-methionine, and were incubated in a binding buffer with GST control, GST-PGC-1 (amino acids 1-190 and 1-190 with a substitution of Leu^{145} to Ala), or GST-PGC-1 (amino acids 1-400) fusion proteins immobilized on glutathione beads. After extensively washing the beads, the [^{35}S]-labeled HNF-4α protein was eluted, separated by SDS-PAGE, and detected by autoradiography. This mutation largely eliminated the binding of PGC-1 to HNF-4α, identifying this motif as a critical mediator of the physical interaction between PGC-1

and HNF-4α. To determine whether the loss of ability of the LXXLL (SEQ ID NO:3) mutant to bind HNF-4α was a specific effect or due to a general loss of proper protein folding, the ability of this mutant to interact with the coactivator SRC-1 was determined. The immunoprecipitation experiments were performed as described above using *in vitro* translated SRC-1. The ability to interact with SRC-1 is unaltered in this mutant, suggesting that the PGC-1-HNF-4α association is indeed mediated by the LXXLL motif (SEQ ID NO:3).

Please replace the paragraph on page 84, starting at line 14, with the following amended paragraph:

LXXLL motifs (SEQ ID NO:3) in coactivators of nuclear receptors have been shown to interact with the carboxy terminal AF-2 domains on the receptors. A radiolabeled C-terminal-deleted HNF-4α gene (the N terminal 360 amino acid residues) lacking the AF-2 domain expressed HNF-4α with no ability to bind to PGC-1. Thus, these data strongly suggest that the interaction between PGC-1 and HNF-4α is mediated by the LXXLL-AF-2 interaction, an interaction that does not require the addition of exogenous HNF-4α ligand. Figure 8 depicts a schematic representation of the interaction domains in PGC-1 and HNF-4α.

Please replace the paragraph on page 84, starting at line 22, with the following amended paragraph:

Interestingly, the LXXLL motif (SEQ ID NO:3) in nuclear coactivators has so far been described only in the context of ligand-dependent interactions with nuclear receptors, because the AF2 domains of receptors require ligand binding to assume the proper conformation needed to interact with the amphipathic α-helices formed from the LXXLL motifs (SEQ ID NO:3). That HNF-4α is able to interact with the LXXLL motif (SEQ ID NO:3) within the PGC-1 molecule in the absence of exogenous ligands is consistent with the well-documented observation that HNF-4α is able to transactivate in transient transfection assays without added ligands.